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|-----------------|-------------|----------------------|---------------------|------------------|
| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
| 09/699,679      | 10/30/2000  | Evan C. Unger        | UNGR-1598           | 8248             |

7590 07/02/2003  
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|                     |
|---------------------|
| EXAMINER            |
| SHARAREH, SHAHNAM J |

|          |              |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
| 1617     |              |

DATE MAILED: 07/02/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/699,679

Applicant(s)

UNGER ET AL.

Examiner

Shahnam Sharareh

Art Unit

1617

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 10 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-35 and 54-60 is/are pending in the application.
- 4a) Of the above claim(s) 5, 12 and 13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-11, 14-35 and 54-60 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 21, 24.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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### DETAILED ACTION

Claims 1-35, 54-60 are pending. Applicant's election of Group IIXII in Paper No. 22B is acknowledged. Applicant's election of species has further been acknowledged accordingly the search is directed to such species wherein R1 is acyl of 18 carbons, R2 is H, R3 is ethylene, R4 is acyl of 18 carbons, P is PEG-3400 and T is a peptide having sequence CRGDC wherein the two cytosines are linked together via a disulfide linkage. Claims 1-4, 6-11, 14-35 and 54-60 are directed to said species and thus under consideration.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Accordingly, claims 1-35, 54-60 are examined to the extent that they are read on Group XII invention. Other inventions enumerated as Groups I-XI are thus withdrawn as being directed to the non-elected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 5, 12-13 are also withdrawn from further consideration because they are not directed to the elected species.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

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***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-11, 14-35 and 54-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al WO 96/40285 ("WO '285") in view of Ruosiahti et al US Patent 5,536,814 and Siegel et al US Patent 6,086,573.

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WO '285 teaches all elements of the instant compounds within the subgenus of elected group (see claim 136-149, page 179-182; claim 164, page 183). The corresponding functional groups in the compounds of WO '285 are as follows:

| Functional Group of the Instant Compound | Instantly Elected Species                                   | Functional Group of the Compounds of WO '285 | Corresponding Subgenus   | Citation   |
|--|---|--|--|--|
| X1, X2                                   | C=X3, C=X3-N(R8), -C=X3-N(R8)-C(=X3)-, wherein X3 is O or S | X2, X3                                       | R5-X4-C(=X5)-, R5-C(=X5)-X4, -X4-C(=X5)-R5, R5-X4-C(=X5)-R5-C(=X5)-X4, wherein X1 is NR4, R3 is a H, R4 is an alkyl 1-10 carbons, R5 is a direct bond, X4 is O, NR4 or S, and X5 is O or S | Page 179, lines 15-22, 25-27.<br>Page 180, lines 1-5     |
| R3                                       | Alkelene  | R2   | Alkelene of 1 to 30 carbons  | Page 180, line 1   |
| R1, R2                                   | Acyl of 18 carbons  | R1   | Alkyl of 1-50 carbons  | Page 179, line 27  |
| P  | Peg-3400  | Z  | Hydrophilic polymer, such as PEG, preferably having MW of about 2000-5000  | Page 179, line 25. page 44, lines 1-6                    |
| T  | CRGDC peptide   | Q  | Cyclic peptides  | Page 179, line 26. page 183, line 13-15. pages 50, 55-58 |

Examiner draws Applicant's attention to WO' 285 claim 135 at page 179.

Accordingly, when X1 is NR4 and R4 is alkyl of 1-10 carbons, WO '285 teaches the subgenus of compounds that encompass compounds of claim 1 and 54 of invention Group XII. Specifically, WO '285 teaches that cyclic peptides can be used as targeting agents. WO' 285 also teaches that such compounds are used to prepare targeted vesicles wherein said vesicles such as liposomes comprising a phospholipid, perfluorobutane gas, and a bioactive agent. See page 29-30; page 90, lines 15-page 91, lines 11; page 108, lines 17-page 109, lines 32 examples 18-21, 37; claims 1-30).

WO'285 appears to only lack the explicit use of CRGDC as the targeting agent, PEG-3400 as the hydrophilic polymer, and urokinase as the bioactive agent.

Ruoslahti is used to show that CRGDC is a cyclic peptide and a suitable targeting agent for recognizing fibronectin- and vitronectin-binding integrins of cell surface. Specifically, Ruoslahti teaches that CRGDC motif include the following amino acid sequences of cys-arg-gly-asp-cys (see abstract, col 2, lines 35-41; Seq ID 10, col 15) which is the same as the instant targeting agent CRGDC.

Siegel is used to merely show that combination of a thrombolytic agent such as urokinase with a gaseous ultrasound contrast agent enhance thrombolytic effects of the thrombolytic agent. (see abstract, col 6, line 65-col 8, line 20).

Accordingly it would have been obvious to one of ordinary skill in the art at the time of invention to employ compounds of WO '285 with PEG-3400, because as suggested by WO'285 patent itself the average MW of PEG of choice must be within 2000-5000. Further, it would have been obvious to substitute the RGD targeting agent of WO '285 patent with CRGDC of Ruoslahti, because WO '285 itself suggested the such cyclic peptides are suitable targeting agents. Thus, the ordinary skill in the art would have had a reasonable expectation of success to prepare suitable compounds as for use in preparing targeted vesicles.

Furthermore, as suggested by Siegel use of urokinase with a gaseous contrast agent shows beneficial clinical results, accordingly, using urokinase in combination with said targeted vesicles would have been obvious, because there would have been

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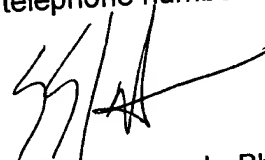
reasonable expectation of success, as explained by Siegel, to improve thrombolytic activity of urokinase.

**Conclusion**

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahn timer Sharareh whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 703-308-1877. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.



Shahn timer Sharareh, PharmD  
Patent Examiner  
Art Unit 1617

SS  
June 26, 2003